23. (Amended) A kit comprising a package containing the pharmaceutical composition of claim 1 and instructions for use thereof for the prevention of epithelial cell damage and repair of epithelial cells.

39. (Amended) The method of claim [38] 37, wherein the epithelial tissue comprises one selected from the group consisting of skin, gastric lining, and intestinal lining.

Please add the following new claims:

--52. (New) The pharmaceutical composition of claim 1, wherein the first polypeptide is PDGF BB dimer and the second polypeptide is $KGF_{des1-23}$.

53. (New) The method of claim 13, wherein the PDGF is PDGF BB dimer and the KGF is $KGF_{des1-23}$.--

REMARKS

Claims 1-15, 23, 25-44 and 49-51 were examined in the Office Action dated December 1, 1997 (Paper No. 11) and rejected under (1) 35 U.S.C. §112, second paragraph as indefinite (claims 13-15 and 39-42); (2) 35 U.S.C. §112, fourth paragraph as failing to further limit the subject matter of the base claim (claim 23); (3) 35 U.S.C. §102(e) as anticipated (claims 1-10, 12-15, 23, 25, 26, 29, 30, 33, 35, 37, 43, 49 and 51); and (4) 35 U.S.C. §103 as obvious (claims 11, 27, 28, 31, 32, 34, 36, 38-42, 44 and 51). These rejections are believed to be overcome by the foregoing amendments and are otherwise traversed for the reasons discussed below.

Overview of the Above Amendments and New Claims:

The specification has been amended to add a claim for priority from the provisional applications from which the present application derives.

The specification has also been amended at page 7, line 23, to insert material previously incorporated by reference from International Publication No. WO 95/01434. (See, page 7, lines 6-8 of the application.) A copy of the cover page of the publication accompanies this response for the Office's convenience.

The claims have been amended to recite the subject invention with greater particularity. Claim 13 now recites that the method entails applying PDGF and KGF and that the PDGF is in a pharmaceutical composition and the KGF is in a pharmaceutical composition. Claim 14 specifies that the "PDGF and KGF are present in the same composition." Claim 23 recites the presence of a "package" and claim 39 has been amended to depend from claim 37 rather than claim 38. Support for the foregoing amendments may be found in the claims as filed as well as throughout the specification at, *inter alia*, page 13, line 10.

New claims 52 and 53 have been added and recite that the PDGF is "PDGF BB dimer" and that the KGF is "$KGF_{des1-23}$." Support for the new claims can be found at, e.g., page 7, lines 6-23.

No new matter has been added to the application by way of the foregoing amendments and new claims.

Rejections Under 35 U.S.C. §112, Second Paragraph:

Claims 13-15 and 39-42 were rejected under 35 U.S.C. §112, second paragraph as indefinite. In particular, claim 13 was considered unclear for failure to specify that the KGF was included in a pharmaceutical composition and

claim 14 was held indefinite based on the lack of antecedent basis for the recitation "the pharmaceutical composition KGF." Claim 13 has been amended to add the term "pharmaceutical" with respect to the KGF composition, thus providing proper antecedent basis for claim 14. This rejection has therefore been overcome.

The Office also requested clarification as to whether the PDGF and KGF recited in claim 14 were present in one composition or separately present in the same carrier or diluent. Claim 14 has been amended to clarify that the PDGF and KGF are present in a single composition. Thus, this basis for rejection has also been overcome.

Finally, claims 39 and 40 were rejected as being duplicative. Claim 39 has been amended to depend from claim 37 rather than claim 38. Accordingly, this rejection has also been overcome.

Rejections Under 35 U.S.C. §112, Fourth Paragraph:

Claim 23 was rejected under 35 U.S.C. §112, fourth paragraph for failing to further limit the subject matter of claim 1, from which claim 23 depends. The Office alleges that the kit "must recite more than one element, and give the relationship between the elements." Office Action, page 3. Claim 23 has been amended to recite that the kit comprises "a package containing the pharmaceutical composition of claim 1..." Accordingly, this basis for rejection is believed to be overcome. Withdrawal thereof is respectfully requested.

Rejection Under 35 U.S.C. §102(e):

Claims 1-10, 12-15, 23, 25, 26, 29, 30, 33, 35, 37, 43, 49 and 51 were rejected under 35 U.S.C. §102(e) as anticipated by U.S. Patent No. 5,624,893 to Yanni et al.

("Yanni"). The Office alleges that Yanni "teaches compositions and methods for treating corneal haze due for example to scar formation (col.7, lines 42-47) or altered wound healing (col.8, lines 52-56)" and that the compositions can comprise "PDGF-BB, PDGF-AA, PDGF-AB, KGF, IGF-I and IGF-II (col.7, lines 42-47)." Office Action, page 3. However, applicant does not agree that the present claims are anticipated by the cited art.

Yanni pertains to the use of topical ophthalmic compositions for treating corneal haze and pain following laser irradiation. The exemplified compositions in Yanni contain bradykinin antagonists or neurokinin-1 antagonists. Although the passages cited by the Office specify that wound healing modulators may be used in the compositions, these passages only name the modulators in a laundry list of compounds and do not disclose the specific combinations encompassed by the present claims. Hence, dozens of conceivable combinations could be formulated from the list of components given at column 7, lines 45-48 of Yanni.

Case law makes clear that where a reference does not highlight a claimed mixture among the many dozen disclosed or suggested, the reference is not sufficient to anticipate claims reciting the specific combination. *In re Kollman* et al., 201 USPQ 193 (CCPA 1979). Furthermore, anticipation cannot be made out by hindsight selection based on an applicant's disclosure of variables of a broad generic disclosure. *In re Ruschig et al.*, 145 USPQ 274 (CCPA 1965). Thus, a generic formula that encompasses a large number of compounds does not describe and therefore anticipate, all of the compounds embraced by the generic teaching merely because they are within the scope of the formula. *In re Petering et al.*, 133 USPQ 275 (CCPA 1962). See, also, *Akzo N.V. v. U.S. Int'l Trade Commission*, 1 USPQ2d 1241, 1246

(Fed. Cir. 1986): (There is no anticipation if to arrive at the claimed invention one must randomly "pick and choose among a number of different polyamides, a plurality of solvents and a range of inherent viscosities.") Accordingly, since Yanni does not specifically call out or suggest applicant's particular combinations from the laundry list of possible substituents described, Yanni cannot anticipate the present claims. Withdrawal of this basis for rejection is therefore respectfully requested.

Rejections Under 35 U.S.C. §103:

Claim 11 was rejected under 35 U.S.C. §103, as unpatentable over Yanni in view of Danilenko et al., *Am. J. Path.* (November 1995) 147:1261-1277 (Danilenko") and Lynch et al., *Proc. Natl. Acad. Sci. USA* (1987) 84:7696-7700 ("Lynch"). However, applicant respectfully submits that this combination is improper.

In this regard, Danilenko is not prior art to claim 11 and is therefore not properly citable in the combination. In particular, the publication date of Danilenko, November 1995, postdates applicant's parent application serial no. 60/005,075, filed October 11, 1995. The priority application clearly discloses the use of PDGF and KGF polypeptides as claimed. Thus, the cited combination is improper and this basis for rejection should be withdrawn.

Additionally, claims 27, 28, 31, 32, 34, 36, 38-42, 44 and 51 were rejected under 35 U.S.C. §103, as unpatentable over Yanni, Danilenko and Lynch, as above, and further in view of Jyung et al., *Surgery* (1994) 115:233-239. Yanni is said to teach a method of treating scar formation and lesions of the cornea using PDGF, KGF and IGF. The Office acknowledges that Yanni does not specifically teach skin repair. However, Danilenko is said to teach a method

for repairing skin using a combination of PDGF and KGF and is said to suggest "strategies including additional combinations or recombinant growth factors being useful for significant acceleration of wound repair." Office Action, page 5. Lynch is cited for teaching "a method for wound healing using a combination of IGF-I and PDGF." Office Action, page 5. The Office notes that none of Yanni, Danilenko or Lynch describes the use of IGFBP but cites Jyung as teaching that the combination of IGF-I with IGFBP-I has "a potent effect on wound healing in rats." Office Action, page 6. However, as with the combination above, applicant respectfully submits that the present combination is improper.

As explained above, Danilenko is not believed to be properly citable against the instant claims. Danilenko, at best, describes the combination of KGF and PDGF. However, applicant was in possession of at least as much of the invention as described in Danilenko prior to the publication date thereof. Accordingly, applicant's invention clearly predates Danilenko and this reference is not properly citable against the present claims. Thus, the cited combination must fail and this basis for rejection should be withdrawn.

Assuming, *arguendo*, that the combination is proper, the combination still does not serve to render claims directed to compositions with KGF, PDGF, IGF and IGFBP, and methods of using these polypeptides together obvious. Although the references individually may disclose pieces of the combination, none of these references gives either a suggestion or an expectation of success for the use of a combined formulation as claimed. It is axiomatic that both the suggestion and expectation of success must be present in the prior art in order for the Patent Office to make out a

prima facie case of obviousness. *In re Dow Chemical Co.*, 5 USPQ2d 1529, 1531 (Fed. Cir. 1988).

In fact, it is well known that mixtures of therapeutic agents can fail to be as effective as individual components due to physical interactions of the individual agents which might result in altered conformation, aggregation or precipitation. Competition between component substances is also known to occur. Indeed, the FDA requires that the efficacy of mixtures be shown even if the efficacy of the individual components has been demonstrated, further evidencing the unpredictable results obtained with mixtures versus individual agents. As is readily seen, the efficacy of mixed compositions cannot be predicted.

Accordingly, the only conclusion supported by the record is that the rejection was made impermissibly using hindsight reconstruction of the invention. As stated by the Court of Appeals for the Federal Circuit, "[i]t is impermissible to use the claimed invention as an instruction manual or 'template' to piece together the teachings of the prior art so that the claimed invention is rendered obvious." *In re Fritch*, 23 USPQ2d 1780, 1784 (Fed. Cir. 1992). See, also, *In re Fine*, 5 USPQ2d 1596, 1600 (Fed. Cir. 1988): "One cannot use hindsight reconstruction to pick and choose among isolated disclosures in the prior art to deprecate the claimed invention."

Thus, applicant submits that the claimed invention is nonobvious over the art and requests reconsideration and withdrawal of this ground of rejection.

Conclusion

Applicant respectfully submits that the claims are novel and nonobvious over the art and define an invention which complies with the requirements of 35 U.S.C. §112. Accordingly, allowance is believed to be in order and an early notification to that effect would be appreciated.

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